

NDA 21-087

Hoffmann-La Roche, Inc.  
Attention: Linda Robertson, Ph.D.  
Program Manager, Regulatory Affairs  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

Dear Dr. Robertson:

Please refer to your new drug application (NDA) dated April 29, 1999, received April 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tamiflu™ (oseltamivir phosphate) 75 mg capsule.

We acknowledge receipt of your submissions dated:

April 29, 1999	August 17, 1999
May 7, 1999	September 1, 1999 (2)
May 17, 1999	September 7, 1999
June 11, 1999	September 8, 1999
July 20, 1999	October 8, 1999
July 30, 1999	October 13, 1999
August 6, 1999	October 14, 1999
August 16, 1999	October 25, 1999

This new drug application provides for the use of Tamiflu (oseltamivir phosphate) 75 mg capsule for the treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than two days. This indication is based on studies of naturally occurring influenza in which the predominant infection was influenza A; and influenza challenge studies in which antiviral activity of Tamiflu was supported for influenza A and B.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical in content to the enclosed draft agreed upon on October 27, 1999 and the additional minor wording changes discussed during a teleconference between yourself and Ms. Grace Carmouze on October 27, 1999. At the next printing of the carton label, reference to Gilead Sciences should be deleted (21 §CFR 201.1(h)). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-087." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you of your Phase 4 commitments specified in your submission dated October 25, 1999. These commitments, estimated to be completed by fourth quarter 2000, are listed below.

1. Provide further information on the safety and efficacy of Tamiflu for treatment of influenza in patients with underlying cardiac conditions and/or respiratory illness.
2. Provide further information on the safety and efficacy of Tamiflu for treatment of influenza in elderly patients.
3. Provide further information on the safety and efficacy of Tamiflu for treatment in subjects with influenza B.
4. Provide information on the safety and efficacy of Tamiflu for treatment of influenza in pediatric patients.
5. Collect and report information pertinent to the safety and efficacy of Tamiflu when used for re-treatment or treatment of multiple episodes of influenza in the same subjects.
6. Provide further information on the safety and efficacy of prophylactic use of Tamiflu to prevent influenza A or B in general and elderly populations.
7. Provide information on the safety and efficacy of Tamiflu for the interruption of influenza virus transmission.
8. Provide information on the pharmacokinetics and safety of Tamiflu in patients with end-stage renal disease undergoing dialysis.
9. Provide information on the pharmacokinetics and safety of Tamiflu in subjects with hepatic impairment.
10. Provide plans for development of a reliable cell culture assay for influenza virus susceptibility and resistance to oseltamivir.
11. Provide plans and proposals for evaluation of cross-resistance between oseltamivir and zanamivir in influenza virus isolates resistant to either drug obtained from both clinical as well as *in vitro* conditions. The assays should include both phenotypic and genotypic measures that include the entire sequence of neuraminidase and hemagglutinin.
12. Provide a detailed plan and timeline for development and implementation of a resistance surveillance program. This program will include the following elements:
  - Phenotypic and genotypic assays for the existence of resistant variants with mutations in the hemagglutinin.
  - Assessment of antigenic variation of clinical isolates and relationship of this variation to oseltamivir exposure.
  - Exploration of clinical implications of oseltamivir-induced and oseltamivir-dependent variants.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21§CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21§CFR 314.55. We are deferring submission of your pediatric studies until December 2, 2000; although, we understand that these studies may be submitted in the first quarter of 2000. We acknowledge receipt of your pediatric development plans dated September 23, 1999.

As you are aware, pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products, (refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity*, available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)). We acknowledge your "Proposed Pediatric Study Request" (PPSR) dated February 18, 1999. Please refer to the correspondence from the Division dated October 15, 1999, in which we recommended that you resubmit your PPSR to include additional studies. We will reconsider a Written Request pending receipt of your revised PPSR. Please note that satisfaction of the requirements in 21 §CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21§CFR 314.80 and 314.81.

If you have any questions, contact Grace N. Carmouze, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Sandra Kweder, M.D.  
Acting Director  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research